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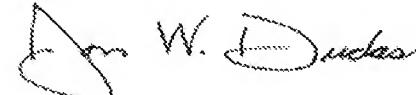
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022404  
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## Mail Stop Provisional Patent Application

PTO/SB/16 (6-95)

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## PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

	Docket Number	4271-25	Type a plus sign (+) inside this box→	+
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## INVENTOR(S)/APPLICANT(S)

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## TITLE OF THE INVENTION (280 characters)

PROCESSES AND SYSTEMS FOR THE EFFICIENT PRODUCTION OF POLYMERIC MICROSPHERES

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## ENCLOSED APPLICATION PARTS (check all that apply)



Specification

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11



Applicant claims "small entity" status.



Drawing(s)

Number of Sheets



"Small entity" statement attached.



Other (specify)

## METHOD OF PAYMENT (check one)



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TYPED or PRINTED NAME

Bryan H. Davidson

REGISTRATION NO.  
(if appropriate)

30,251



Additional inventors are being named on separately numbered sheets attached hereto.

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# ***U.S. PROVISIONAL PATENT APPLICATION***

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                            Janice PHILLIPS  
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*Invention:*      PROCESSES AND SYSTEMS FOR THE EFFICIENT PRODUCTION OF  
                            POLYMERIC MICROSPHERES

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## ***SPECIFICATION***

**PROCESSES AND SYSTEMS FOR THE EFFICIENT  
PRODUCTION OF POLYMERIC MICROSPHERES**

**FIELD OF THE INVENTION**

The present invention relates to processes and systems for the  
5 production of small polymeric particles, conventionally termed  
"microspheres". In especially preferred embodiments, the present  
invention is directed toward processes and systems whereby polymeric  
microspheres may be produced in an efficient and cost-effective manner.

**BACKGROUND AND SUMMARY OF THE INVENTION**

10 Polymeric microspheres (i.e., polymeric particles having an  
average particle size of between about 100 nanometers to about 100  
microns, and typically between about 200 nanometers to about 50  
microns) are being studied in a wide variety of applications including  
pharmaceuticals, coatings, additives for plastics formulations and food,  
15 and agricultural products. While microspheres are currently manufactured  
and sold commercially, widespread implementation of polymeric  
microsphere technology is limited by production costs. Traditional  
dispersion methods of microsphere production involve large amounts of  
volatile organic compounds and waste water and have limited production  
20 output as they are generally batch processes.

25 Dispersion polymerization is currently the primary method for  
making polymeric microspheres. In this regard, a water insoluble vinyl  
monomer is dispersed in water in an oil-in-water emulsion. Liquid  
microspheres are formed in the dispersion process with particle size  
controlled by the oil monomer concentration, surfactant type and

concentration and degree of mixing. Either an oil soluble or water soluble initiator initiates polymerization within the liquid microsphere when the emulsion is heated forming a solid particle.<sup>i</sup> Surfactant-free emulsion polymerization has been achieved by copolymerizing hydrophilic and 5 hydrophobic monomers within the microspheres.<sup>ii</sup> Oil soluble monomers can also be dispersed and polymerized in alcoholic media to form microspheres.<sup>iii</sup>

In a similar manner, water-in-oil emulsions are used to polymerize 10 water soluble monomers. This is commonly used in making microspheres of polyacrylic acid or poly(acrylic acid–co-sodium acrylate).<sup>iv,v</sup>

Acrylic acid is neutralized to a desired degree with aqueous sodium hydroxide. To make a hydrogel microsphere, a crosslinking agent such as N,N'-methylenebisacrylamide is added to the aqueous monomer solution. Potassium persulfate is a water soluble initiator that is generally 15 dissolved in the monomer solution prior to dispersion. Particle size is controlled by the concentration of the aqueous monomer solution, surfactant type and concentration and the degree of mixing. Polymerization occurs within the liquid monomer droplets forming a solid microsphere.

20 Isolating dry microspheres from dispersion polymerization involves filtration and washing leaving large amounts of solvent or water waste. Isolation and waste treatment result in high costs for microsphere production. Solvent-less techniques have been investigated as alternative methods to producing microspheres.

25 Aerosol polymerization has been used to make microsphere via step-growth and chain-growth polymerization techniques. Polysiloxane particles have conventionally been produced using an evaporation-

condensation route where vaporized monomer condense on a nuclei and polymerize when exposed to a second monomer vapor.<sup>vi</sup> A similar method was used to produce polyurea microspheres with diameters of two microns and less.<sup>vii</sup> Unfortunately, evaporation-condensation route

5 produces a low yield of microspheres.

Polystyrene microspheres were produced by nebulizing styrene monomer and introducing the aerosol into a chamber containing a vaporized initiator (trifluoromethanesulfonic acid).<sup>vi</sup> Spherical polystyrene microspheres were produced with diameters of 1-5 microns. Increasing attention has been given to the use of supercritical carbon dioxide as a "environmentally benign" solvent for making microspheres.<sup>viii,ix,x</sup> While potentially an improvement over conventional dispersion polymerization techniques, supercritical CO<sub>2</sub> requires extensive capital equipment to control pressure and temperature.

10 Improvements in the microsphere production process are needed to lower cost and enable widespread use. Therefore, it is one object of this invention to provide processes which enable polymeric microspheres to be produced continuously on a cost-effective basis.

15 Broadly, the present invention is embodied in processes whereby continuous polymeric microspheres are made by nebulizing a solventless initiated monomeric liquid to form an aerosol of desired monomeric liquid droplets within a reaction zone, and allowing the nebulized droplets of the monomeric liquid to polymerize within the reaction zone. The thus polymerized particles may thereafter be collected and removed from the reaction zone for further processing and/or use as may be desired.

20 These and other aspects, advantages and/or objects of the invention will become more clear after careful consideration is given to the

following detailed description of the preferred exemplary embodiments thereof.

**BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS**

5 Reference will hereinafter be made to the accompanying drawings, wherein like reference numerals throughout the various FIGURES denote like structural elements, and wherein;

FIGURE 1 is schematic representation of one embodiment in accordance with the present invention showing a system that may be employed to make polymeric microspheres;

10 FIGURE 2 is a schematic representation of another embodiment in accordance with the present invention showing another system that may be employed to make polymeric microspheres; and

15 FIGURE 3 is a schematic representation of yet another embodiment in accordance with the present invention showing another system that may be employed to make polymeric microspheres.

**DETAILED DESCRIPTION OF THE INVENTION**

A schematic of one presently preferred aerosol polymerization system in accordance with the present invention is shown in accompanying Figure 1. As shown, the aerosol polymerization system is 20 comprised of a modular vertical tube which defines the polymerization zone for the droplets of initiated monomeric liquid in the aerosol. A nebulizer is positioned at the top of the tube so as to create an aerosol of fine droplets from the supply of initiated monomeric liquid and disperse the droplets into the polymerization zone defined by the tube. A collection

plate is positioned at the bottom of the vertical tube to collect and contain the resulting polymeric microspheres.

The temperature within the reaction zone may be elevated by any suitable means. Thus, for example, heated air via an air intake duct may 5 be provided below the collection plate to allow heated air flow from a blower and into the interior of the tube. The tube may optionally or additionally be heated by means of electrical resistance heaters and/or by means of a heat-exchange medium. The heated reaction zone will thus provide a temperature environment for the monomeric droplets that will 10 ensure polymerization during the residence time therein.

As depicted in Figure 1, the nebulizer of the aerosol generator is most preferably placed vertically above the tube so as to direct the resultant aerosol downwardly into the reaction zone. The aerosol will thus flow downwardly within the vertical tube and collect at the bottom plate. 15 The position of the nebulizer could however be positioned at the bottom of the tube as shown in accompanying Figure 2 so as to direct the aerosol flow upwardly within the reaction zone.

The system shown in Figure 2 is preferred for those polymers whereby an increase in the residence time of the aerosol within the 20 reaction zone is desired without increasing the tube length. In this regard, airflow will most preferably be generated down the sides of the wall using a gas diffusion ring. The gas diffusion ring will direct airflow down the sides of the cylinder thereby causing the path of the aerosol rising generally centrally within the tube to be directed toward the periphery of 25 the reaction zone and thereafter descend along the walls of the tube to the collection plate.

Another system configuration in accordance with the present invention is depicted in accompanying Figure 3 and involves the use of a UV initiation mechanism for the aerosol polymerization as opposed to the thermal initiation technique described above. UV initiation of the monomeric liquid may be desirable in that it could minimize (or eliminate entirely) the need to heat the tube thereby resulting in reduced production costs.

The system shown in Figure 3 is similar to that shown in Figure 2, except that one or more ultraviolet (UV) lamps are placed along the wall of the column near the top of the aerosol plume. Aerosol microspheres are therefore propelled out of the aerosol generator through the UV light zone and thereafter fall back through the UV light zone. Using the bottom aerosol generation configuration will thus double the exposure time to the UV light. If desired, the bottom zone can be heated to maintain or increase and/or control the polymerization rate of the monomeric liquid droplets. Airflow is most preferably generated down the sides of the wall using a gas diffusion ring.

Virtually any conventional UV light source may be employed satisfactorily in the present invention. Thus, UV light can be provided by means of a conventional medium pressure mercury lamp operatively positioned with respect to the tube walls. Preferably, there are at least two UV lamps positioned diametrically opposite to one another. In such a manner, therefore, photopolymerization can be conducted in accordance with the present invention by the addition of a photoinitiator to the vinyl monomeric liquid supplied to the aerosol generator.

The process of the present invention therefore results in the manufacture of polymeric microspheres without the use of a solvent which

is amenable to large scale production. Microspheres could then be available in large quantities at a greatly reduced cost as compared to that associated with conventional microspheres. Such reduced costs would therefore make the use of microspheres made by the present invention

5 more conducive for use in a wide range of products in a variety of end-use applications, such as in agriculture (e.g., to assist in the irrigation of soil by use of absorbent polymeric microspheres), medical applications (e.g., microspheres used for the controlled and/or sustained release of a drug or other agent or as an embolic in embolotherapeutic techniques), food

10 packaging (e.g., to trap excess fluids by use of absorbent polymeric microspheres), adhesives, body armor, building and construction (e.g. noise dampening, roof coatings, polymer concrete), paper manufacturing, foams and toys and recreation decorations (e.g., as a component part of commercial display designs, photography and film making products,

15 hobbies, and sports activities).

The present invention will be further understood from the following non-limiting Examples.

### Examples

Acrylic acid (12.99 grams, 0.18 mole) was 37.5% neutralized with

20 13.5 ml of 5M NaOH. N,N'-Methylenebisacrylamide (1.54 grams, 0.01 mole) was dissolved into the acrylic acid/sodium acrylate/water solution. The monomer solution contained 40% by weight water and 60% monomer. A 5% solution of potassium persulfate in water was also prepared. Potassium persulfate is a water soluble free radical initiator

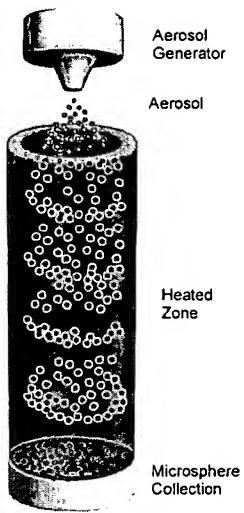
25 with a 10 hour half-life at 60°C in water.<sup>xi</sup> The polymerization solution was prepared by adding 2.7 grams the 5% potassium persulfate solution to

26.032 grams of the monomer solution. The initiator concentration was 1% by weight.

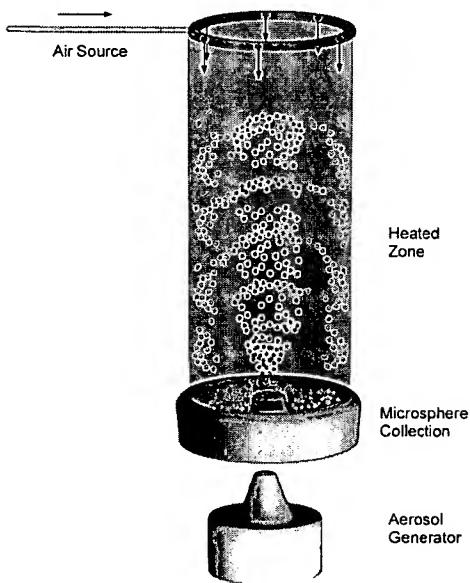
The initiator/monomer solution was then sprayed with a plastic spray bottle through a hole in the oven ceiling through heated air of 50 to 5 80°C onto heated glass plates. The distance from the spray bottle to the plate was approximately 43 cm. The plates were removed 60 seconds after spraying the monomer solution during which time the monomer solution gelled. The slides were observed under a microscope. Microscope observation of the slides revealed a combination of 10 microspheres (irregular shaped) and larger droplets that had not polymerized in the air but impacted the slide and polymerized. Figure 4 is a photograph of microspheres with particle sizes ranging from 12 to 70 microns. A control slide was sprayed outside the oven (i.e. at room temperature) at the same distance and then inserted into the oven for 60 15 seconds. No particles were observed on the control slide.

The experiment described above reveals that initiation and gellation of acrylic acid/sodium acrylate solution occurs rapidly at moderate temperatures. As such, solventless aerosol polymerization of initiated monomeric solutions is possible.

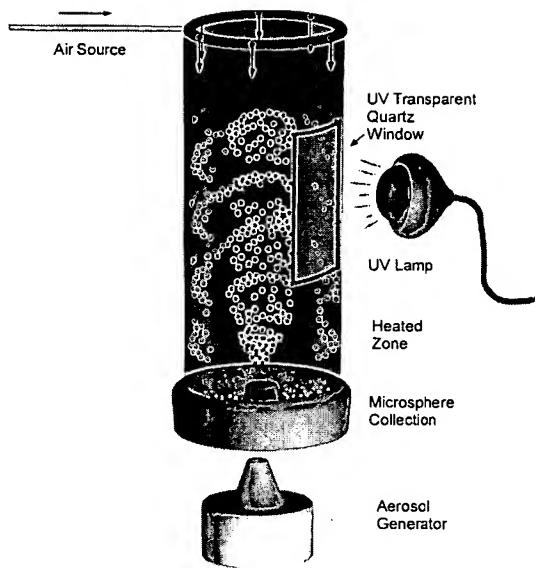
20 Therefore, while the present invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within 25 the spirit and scope of the appended claims.



**Figure 1 - Downflow Aerosol Polymerization Reactor System with Thermal Reactor Zone**

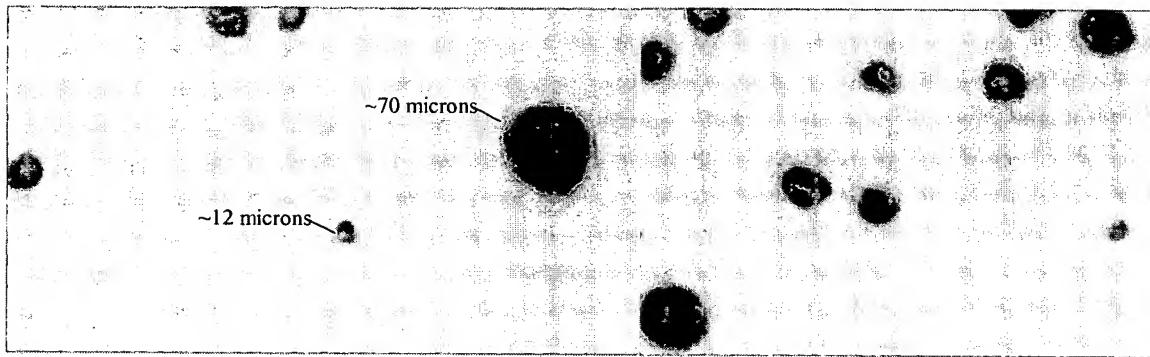


**Figure 2 - Upflow Aerosol Polymerization Reactor System with Thermal Reactor Zone**



**Figure 3 – Upflow Aerosol Polymerization Reactor System with UV Light Reactor Zone**

5



**Figure 4 – Microspheres produced from aerosol polymerization of acrylic acid/sodium acrylate solution. Particles on right have diameters ranging from 20 to 50 microns**

**Cited Publications, the entire content of each being expressly incorporated by reference into the subject application:**

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- <sup>i</sup> K. Suzuki, A. Goto, M. Takayama, A. Muramatsu, M. Nomura, "An Experimental Study on the Kinetics and Mechanisms of Styrene Polymerization in Oil-in-Water Microemulsion Initiated by Oil-Soluble Initiators", *Macromol. Symp.*, **155**, 199-212 (2000).
- <sup>ii</sup> P. Wang and Q. Wang, "Emulsifier-free Emulsion Polymerization of Styrene with Methacrylic Acid", *Appl. Polym. Sci.*, **88**, 1747-1751 (2003).
- <sup>iii</sup> C. Ho, S. Chen, M. Amiridis and J. Van Zee, "Dispersion Polymerization of Styrene in Alcoholic Media: Effect of Initiator Concentration, Solvent Polarity and Temperature on the Rate of Polymerization", *J. Polym. Sci.: Pt. A: Polym. Chem.*, **35**, 2907-2915 (1997).
- <sup>iv</sup> P. Jiang, Z. Zhang and M. Zhang, "Kinetics of the Potassium Persulfate-Initiated Inverse Emulsion Polymerization of Sodium Acrylate Solutions", *J. Polym. Sci.: Pt. A: Polym. Chem.*, **34**, 695-699 (1996).
- <sup>v</sup> C. Mayoux, J. Dandurand, A. Ricard, C. Lacabanne, "Inverse Suspension Polymerization of Sodium Acrylate: Synthesis and Characterization", *J. Appl. Polym. Sci.*, **77**, 2621-2630 (2000).
- <sup>vi</sup> D. Shin, E. Oh and S. Kim, "Preparation of Polymer Particles in Aerosol-Phase Reaction", *Aerosol Science and Technology*, **24**, 243-254 (1996).
- <sup>vii</sup> R. Partch, K. Nakamura, K. Wolfe and E. Matijevic, "Preparation of Polymer Colloids by Chemical Reactions in Aerosols", *Journal of Colloid and Interface Science*, **105**(2), 560-569 (1985).
- <sup>viii</sup> K. Matsuyama, K. Mishima, H. Umemoto and S. Yamaguchi, "Environmentally Benign Formation of Polymeric Microspheres by Rapid Expansion of Supercritical Carbon Dioxide Solution with a Nonsolvent", *Environmental Science and Technology*, **35**, 4149-4155 (2001).
- <sup>ix</sup> M. Okubo, S. Fujii, H. Maenaka and H. Minami, "Production of Polyacrylonitrile Particles by Precipitation Polymerization in Supercritical Carbon Dioxide", *Colloid and Polymer Science*, **281**, 964-972 (2003).
- <sup>x</sup> J. Jung and M. Perrut, "Particle Design Using Supercritical Fluids: Literature and Patent Survey", *Journal of Supercritical Fluids*, **179**, 219 (2001).
- <sup>xi</sup> [www.sigmaaldrich.com/img/assets/3900/thermal\\_initiators.pdf](http://www.sigmaaldrich.com/img/assets/3900/thermal_initiators.pdf).